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Research Progress Based on Serious Complication of Stroke in Patients with Chronic Kidney Disease

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Abstract

Patients with chronic renal insufficiency (CKD) in the uremic stage can suffer various degrees of damage to various organ systems throughout the body, with the nervous system being common and severe. Chronic kidney disease (CKD) complicated with stroke has a high incidence and poor prognosis, which brings a heavy burden to patients and society. Understanding the risk factors of uremic patients complicated with stroke and taking preventive measures as soon as possible is of great significance for controlling the progress of the disease. The risk factors of uremic patients complicated with stroke are complex and diverse. Traditional risk factors include hypertension, diabetes, atrial fibrillation, dyslipidemia, etc. Non traditional risk factors such as genetic susceptibility, uremia, anemia, mineral and bone abnormalities can also promote the occurrence of stroke. In addition, dialysis related risk factors such as insufficient cerebral perfusion, increased arterial stiffness, and increased blood pressure variability can also cause stroke. Therefore, it is important to identify the risk factors of stroke in uremic patients as early as possible and take targeted preventive measures.

Keywords: chronic kidney disease, uremia, stroke, hypertension, hemodialysis, risk factors

1. Introduction

Chronic kidney disease (CKD) affects 8% to 16% of the world's population (Jha V, Garcia-Garcia G, Iseki K, et al., 2013), and more than 90% of patients with advanced CKD require hemodialysis (HD) to keep them alive. CKD is a definite risk factor for cardiovascular and cerebrovascular diseases (Toyoda K, & Ninomiya T., 2014). Compared with the general population, CKD has a higher probability of stroke and other cardiovascular and cerebrovascular diseases, and its condition is more serious. It has been reported in the literature that the incidence of stroke in advanced CKD patients is much higher than that in the general population. Among them, hemorrhagic stroke in hemodialysis patients has a poor prognosis with a fatality rate of 50%-90%, which is a common cause of death in CKD patients (Kim K R, & Kim Y Z., 2013). Therefore, how to prevent and treat stroke in CKD patients

and reduce mortality has become a research focus of related disciplines.

2. The Relationship Between CKD and Stroke

The incidence of cerebrovascular disease is higher in patients with CKD than in the healthy population, and higher in patients with advanced dialysis. Recent studies have shown that CKD is not associated with known traditional cardiovascular risk factors, but is an independent risk factor for stroke, subclinical cerebrovascular abnormalities, and physical and cognitive decline (Toyoda K., 2015). Low glomerular filtration rate is a risk factor for higher incidence of ischemic and hemorrhagic stroke. A meta-analysis of 83 studies (over 2 million participants) (Masson P, Webster A C, Hong M, et al., 2015) showed a negative linear relationship between glomerular filtration rate (GFR) and stroke risk, with a 7% increase for every 10 mL/(min·1.73 m2) reduction in GFR. Increased urinary albumin to creatinine ratio (ACR) by 25 mg /mmol was associated with a 10% increased risk of stroke. Results were consistent across subtypes of stroke, gender, or prevalence of vascular risk factors (hypertension, diabetes, and smoking), suggesting an independent relationship between CKD and stroke risk.

3. Traditional Risk Factors for Stroke in Patients With CKD

Due to the similar and fragile microvascular regulation of the kidneys and brain, the strain vessel hypothesis of hypertensive vascular injury is considered to be a possible mechanism for the connection between CKD and stroke (Ito S, Nagasawa T, Abe M, et al., 2009). The kidney and brain are both high-volume, low vascular resistance systems, and depend on local self-regulation, so these two organs are vulnerable to multiple traditional risk factors such as hypertension, diabetes, atrial fibrillation, dyslipidemia, excessive salt intake, carotid artery disease, heart failure, obesity and so on.

3.1 Hypertension

Renal hypertension is one of the common complications in patients with CKD, with an incidence of more than 60% (Muntner P, Anderson A, Charleston J, et al., 2010). Both the kidney and the brain are regulated by fragile and similar microvessels. In the occurrence of hypertension, the glomerular sclerosis is easy to occur in the proximal medullary arterioles of the kidney, which leads to the progressive decline of renal function and the deterioration of systemic hypertension. At the same time, the perforator artery of the brain is prone to lipid hyaluronic degeneration, and the local blood flow is reduced, leading to the occurrence of stroke. Yano et al. (Yano Y, Hoshide S, Etoh T, et al., 2011) proved that CKD was an independent predictor of stroke in hypertensive patients, and CKD and norepinephrine levels synergistically increased the risk of stroke. Hypertension is an important and controllable risk factor for stroke, and CKD patients are commonly associated with hypertension. Therefore, more attention should be paid to blood pressure control than normal people. The Global Organization for Improving the Prognosis of Kidney Diseases recommends that blood pressure in CKD patients be controlled below 120/80 mmHg, and that renin angiotensin system blockers be first promoted to prevent stroke (KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease, 2021).

3.2 Diabetes

Kidney is the main organ affected by microvascular disease in diabetes, and the incidence rate of CKD in diabetes population is about 36% (Kelly D, & Rothwell P M, 2020). The glomerulus of diabetes patients is in a state of hyperfiltration for a long time, which causes glomerular hypertrophy and thickening of basement membrane, and then forms proteinuria, leading to glomerulosclerosis and arteriolar lesions, and finally leading to stroke. CKD patients with diabetes should actively screen and control their blood sugar in clinical practice, strictly follow the dietary guidelines for diabetes, and recommend that CKD patients with diabetes and eGFR>30 ml/ (min ·1.73 m2) use sodium glucose cotransporter 2 inhibitors to prevent stroke (KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, 2020).

3.3 Excessive Salt Intake

Salt is essential for regulating blood pressure, blood volume, osmotic pressure, and pH. It is the main sodium substance that the human body consumes. High salt status can lead to endothelial dysfunction and atherosclerosis, leading to fibrosis and decreased elasticity of the major arteries (Li Y, Huang Z, Jin C, et al., 2018; Hu M, Lin Y, Men X, et al., 2021). A prospective community-based cohort study showed that

people with moderate salt intake (2 400 to 4 000 mg /d) had a 23% higher risk of stroke than those with low salt intake (< 2 400 mg /d), and salt intake was positively correlated with stroke risk (Li Y, Huang Z, Jin C, et al., 2018). However, due to the inadequate concept of salt restriction, the majority of Chinese people do not pay attention to and strictly limit salt in their daily life, which leads to persistent hypertension in CKD patients and increases the risk of stroke.

3.4 Obesity

With the improvement of people's living standards and changes in dietary structure in today's society, the incidence of obesity is becoming higher and higher, and there is also a trend towards an increase in CKD patients. A prospective cohort study showed that weight, body mass index, waist circumference, waist height ratio, waist hip ratio and other obesity indicators were significantly related to the incidence rate of CKD, indicating that obese people had a higher risk of CKD (Memarian E, Nilsson P M, Zia I, et al., 2021). Although studies have shown that obesity is positively correlated with the incidence of CKD, the mechanism by which obesity affects CKD remains unclear, which may be related to hemodynamics, metabolic changes and lipid nephrotoxicity (Yim H E, & Yoo K H., 2021). Obesity is an established risk factor for hypertension, diabetes and dyslipidemia, and plays an important role in the pathogenesis of stroke. The increased levels of various cytokines and chemokines in the excess adipose tissue of obese patients increase the risk of stroke through the direct effect of vascular endothelial injury, promoting thrombosis and atherosclerosis, as well as the indirect effect of increasing the incidence of hypertension, diabetes and dyslipidemia. A large prospective cohort study showed a dose-response relationship between body mass index, waist circumference, waist-height ratio and stroke (Liu S, Gao Z, Dai Y, et al., 2020). For obese CKD patients, emphasis should be placed on monitoring, healthy diet and regular exercise, so as to prevent stroke.

4. Non-Traditional Risk Factors for Stroke in Patients with CKD

At present, traditional risk factors have been unable to fully explain the high risk of stroke in CKD patients, and more attention has been paid to non-traditional risk factors such as uremia, anemia, genetic predisposition, mineral and bone abnormalities, oxidative stress, chronic inflammation, and endothelial dysfunction.

4.1 Uremia

Uremia is the terminal stage of the development of various acute and chronic renal diseases, which eventually leads to severe renal failure and the inability to discharge excess water, electrolytes and various toxins from the body in a timely manner (Liu Hongmei, 2022). At present, clinical treatment of uremia is mainly based on hemodialysis, which can replace renal function to a certain extent and reduce the serum urea nitrogen (BUN) and serum creatinine (Scr) levels of patients, thus relieving clinical symptoms of patients (Zhang Wenge, Li Qiang, Liu Cui, et al., 2017). However, hemodialysis cannot completely replace kidney function. Clinically, even if patients can achieve adequate dialysis, there are still some residual toxins, especially medium and macromolecular toxins, lingering in the body, resulting in poor stomach, fatigue, anemia, pruritus and other symptoms. Some patients may even develop uremic cardiomyopathy, uremic encephalopathy, uremic related peripheral neuropathy and other complications (Ruan Mengying, Jin Minggong, Fang Wenqing, et al., 2019). Kidney, brain and heart are both organs with small vascular distribution, which share similarities in terms of anatomy and physiological mechanism, and share common traditional vascular risk factors. When cerebral infarction occurs in the brain stem or ventricle and has a large infarct area, it will seriously threaten the life safety of patients with maintenance hemodialysis (Hu Yongwei, Min Qunyan, & Shao Min, 2020).

4.2 Anemia

Renal anemia is a common complication of CKD patients, and more than 50% of CKD patients in China are complicated with anemia (Zheng Ke, & Li Xuemei, 2020). CKD patients are often accompanied by varying degrees of iron deficiency, iron metabolism disorders, and reduced erythropoietin production, which can easily lead to anemia. Previous studies believed that anemia was a risk factor for cardiovascular events in patients with CKD, and the relative risk of cardiovascular events decreased by about 17% for every 10 g /L increase in hemoglobin (Li Jinlong, Hu Yugang, & Zhou Qing, 2022). In the condition of anemia, the oxygen-carrying capacity of blood decreases, resulting in the decreased oxygen supply of tissues and organs

in CKD patients, the compensatory increase in cardiac output of the body, the up-regulated expression of vascular endothelial cell adhesion molecules, triggering the inflammatory response to form thrombosis, and thus stroke (Heo J, Youk T M, & Seo K D., 2021). To prevent the occurrence of stroke, CKD patients should pay attention to anemia as soon as possible and receive treatment with heme stimulating hormone. However, excessive treatment of anemia can increase the risk of stroke. Studies by Mimura et al. (Mimura I, Tanaka T, & Nangaku M., 2015) have shown that correcting anemia to hemoglobin>130 g/L does not bring additional benefits from cardiovascular events, and excessive hemoglobin levels increase the risk of myocardial infarction, heart failure, and stroke. Therefore, in the process of anemia treatment in CKD patients, it is necessary to determine the target hemoglobin value according to the specific conditions of patients, and timely start alternative therapy, while avoiding excessive correction of anemia, so as to reduce the occurrence of stroke.

5. Dialysis-Related Risk Factors of Stroke in CKD Patients

With the improvement of dialysis technology, the survival period of patients continues to extend, but the mortality rate of patients due to various complications caused by dialysis treatment remains high. Stroke is the leading cause of cardiovascular death in dialysis patients (Luo Z M, Liu M Y, He F, et al., 2017). In addition to traditional and non-traditional risk factors, a series of dialysis-related risk factors (such as cerebral hypoperfusion, increased arterial stiffness, increased blood pressure variability and dialysis mode) also promote the occurrence of stroke (Weng Yu, Ma Tieliang, & Zhao Yanping, 2022). Compared with the general population, the autonomic nervous function of hemodialysis patients is less sensitive to pressure reflex, so they are less able to tolerate acute blood pressure drop during dialysis ultrafiltration (Burton J O, Jefferies H J, Selby N M, et al., 2009). Blood pressure control is more complicated in dialysis patients, and some studies have linked reduced blood pressure to adverse outcomes, including increased mortality, especially in older or diabetic patients, or those with a history of heart disease. In a study of 58 hemodialysis patients, ischemic events increased 3% for every 10 mmHg decrease in mean arterial pressure (MAP) (Macewen C, Sutherland S, Daly J, et al., 2017). At present, the optimal time to start dialysis is still controversial. It is recommended to select the time to start dialysis and the appropriate dialysis mode according to the comprehensive evaluation of patients' eGFR and clinical symptoms, so as to reduce the occurrence of stroke.

6. Treatment of CKD Combined with Stroke

The US National Stroke Guidelines (GWTG Stroke) Registry analyzed the relationship between CKD and major bleeding outcomes after intravenous rTPA in acute ischemic stroke and found that compared with patients with normal renal function, CKD patients had higher hospital mortality and poorer discharge status, not due to the presence of bleeding. It is related to other adverse factors such as heart failure and uremic encephalopathy caused by chronic kidney disease (Ovbiagele B, Smith E E, Schwamm L H, et al., 2014). So CKD itself is not contraindicated to become venous rTPA in eligible patients, especially from the point of view of bleeding risk. Due to the greatly increased risk of stroke and poor outcomes, it is particularly important to better target the traditional risk factors, non-traditional risk factors and dialysis-related risk factors for stroke in CKD patients to apply active and effective prevention strategies to reduce the stroke rate in this vulnerable patient population.

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